



ORIGINAL RESEARCH PAPER

Biochemistry

SERUM FETUIN -A LEVELS IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS PATIENTS

KEY WORDS: Serum Fetuin-A, Type 2 Diabetes Mellitus, Insulin Resistance

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ABSTRACT

Introduction: Serum fetuin-A is a multifunctional circulating glycoprotein which inhibits the insulin receptor tyrosine kinase activity and induces a low grade inflammation which results in insulin resistance. High levels of fetuin-A are associated with insulin resistance.
Materials & Methods: The present study included 100 cases and 100 age matched healthy controls, visiting medical outpatient department of SGT Medical College and Hospital, Haryana.
Results: The mean FPG, PPBG, TC, TG, VLDL, LDL, HbA1c and serum fetuin-A levels were significantly higher in diabetic group compared to controls. Serum fetuin-A is positively correlated with FBG, HbA1c, TG, TC, and VLDL and negatively correlated with HDL in diabetic patients as compared to healthy controls.
Conclusion: This study concluded that serum fetuin-A is significantly elevated in T2DM patients and it indicates that serum fetuin -A may play a role in pathogenesis of diabetes by inhibiting insulin receptor tyrosine kinase and insulin signalling.

Introduction

The rapidly increasing prevalence of diabetes mellitus world-wide is one of the most serious and challenging health problems in the 21st century. The number of people with diabetes grows faster than expected. In 2007, 246 million people (roughly 6%) were affected world-wide and it is estimated that this will increase to 380 million, or 7.3% by 2025. Furthermore, it is estimated that there are even more people (308 million or 8.1%) with impaired glucose tolerance (IGT). These people have a significant risk of developing type 2 diabetes mellitus (T2DM).¹

Diabetes is a metabolic disorder which is characterized by hyperglycemia and glucose intolerance due to insulin deficiency, impaired effectiveness of insulin action or, both.¹

Type 2 diabetes is characterized by inadequate insulin secretion and insulin resistance in the target tissues.² Genes and environment both contribute to the development of disease.³ Insulin mediates its actions through phosphorylation of the insulin receptor (IR), a transmembrane-spanning tyrosine kinase (TK) receptor. Binding of insulin to the IR activates its intrinsic TK activity and, subsequently, tyrosine phosphorylation of several substrates, such as insulin receptor (IRS) and Shc, which mediate the metabolic and mitogenic effects of insulin.⁴ Various factors, including fatty acids and cytokines, have been shown to influence the effect of insulin through insulin-signalling molecules or through other pathways that interfere with the insulin-signalling pathway.⁵

Among several pathway involved in the pathogenesis of the epidemically spreading disease type 2 diabetes an altered secretory pattern of the expanded and inflamed adipose tissue is thought to be important for the regulation of insulin sensitivity and subclinical inflammation in various tissues.⁶ In analogy to deregulated adipose tissues there is increasing evidence that non-alcoholic fatty liver disease, which predictive of metabolic disease, is also associated with an altered secretory pattern of proteins, which can be referred to as hepatokines, and which are both markers of the disease, and are involved in its pathophysiology.⁷ Among them fetuin-A gained much attention during the recent years because of its association with type 2 diabetes and cardiovascular disease risk and its important role in the pathogenesis of insulin resistance and subclinical inflammation.⁸⁻¹⁰

Fetuin-A, also known as alpha 2 -Heremans Schmid glycoprotein (AHSG), is an abundant plasma protein synthesized predominantly in the liver. Fetuin-A regulates calcium homeostasis and inhibits IR autophosphorylation, which is mediated by its intrinsic TK

activity.¹¹ The human AHSG gene is located at chromosome 3q27, which has been identified as a susceptibility locus for type 2 diabetes and metabolic syndrome.¹² Recently, epidemiological studies showed that serum fetuin-A was associated with insulin resistance and its co-morbidities, such as metabolic syndrome and type 2 diabetes.¹³

The aim of this study was to investigate the association between serum fetuin-A levels with FPG, PPBG, HbA_{1c} and lipid profile in newly diagnosed type 2 diabetes patients.

Materials & Methods

The study was carried out in the Department of Biochemistry and the Department of Medicine at SGT Medical College and Hospital, Budhera, Gurugram. 100 Patient with newly diagnosed Type 2 DM in age group >30 years both male and female were included in the study and 100 age matched healthy subjects were taken as control. Written informed consent was taken from all individuals who are willing to participate in this study. This study was conducted after getting ethical clearance by institutional ethical committee.

Inclusion Criteria: Clinically and biochemically newly diagnosed T2DM patients in the age group of >30 years.

Exclusion Criteria:

- Acute complications of diabetes
- Renal Dysfunction
- Hepatic Dysfunction
- Non Alcoholic fatty liver diseases
- Patients on any medication known to cause hyperglycemia

Controls: Healthy controls in the age group of >30 years.

Blood sample was taken after an overnight fast and serum was analyzed for the biochemical parameters FBG, PPBG, HbA_{1c}, TC, TG, LDL, VLDL, HDL and Fetuin-A. Serum Fetuin-A was estimated by ELISA method.

Statistical Analysis

Data was collected and mean ±SD for all the parameters was calculated. The results were analysed statically using SPSS software version 21.0. The magnitude of inter group differences for each of parameters was determined by student's t test. A p-value of <0.05 was considered significant and p-value >0.05 as non-significant. Pearson's correlation coefficient is used for finding the correlation between various parameters.

Results

The present study was conducted on 100 patients of type 2 diabetes mellitus in the age group of >30 years. Several clinical characteristics and biochemical parameters were compared among the patients and a control group of 100 age matched healthy subjects. Age, BMI, WHR & biochemical parameters FBG, PPBG, HbA1c, Lipid profile (TC, TG, VLDL, LDL, HDL) & serum fetuin-A of diabetic patients and controls are given in **Table: 1**

Table 1: The comparison between age, BMI, WHR and biochemical parameters in healthy controls and T2DM patients

Biochemical Parameters	Control (n=100) Mean± SD	Diabetic (n=100) Mean± SD	p value
Age	52.19±2.58	51.46±3.78	0.109
BMI	20.39±0.71	34.78±1.74	<0.001
WHR	0.81±0.06	1.09±0.04	<0.001
FBG	87.28±6.15	283.73±27.48	<0.000
PPBG	121.09±6.67	271.63±19.74	<0.000
HbA1c	5.08±0.44	9.25±0.63	<0.001
TC	170.98±11.44	290.34±26.85	<0.000
TG	119.23±15.39	328.11±40.89	<0.000
VLDL	23.84±3.08	52.80±5.37	<0.001
LDL	113.31±7.61	166.72±13.47	<0.001
HDL	40.28±5.05	33.19±5.07	<0.001
Fetuin-A	154.11±7.05	354.29±26.48	<0.001

Mean ±SD of age among cases and controls were 51.46± 3.78 years and 52.19± 2.58 years respectively. There was no significant difference with respect to age distribution in cases and controls (p>0.05). BMI and WHR are significantly higher in T2DM patients than controls. Significantly elevated levels of fasting and postprandial blood glucose and glycated haemoglobin were observed in T2DM patients as compared to controls. Dyslipidemia is also seen in T2DM patients. Lipid parameters serum total cholesterol, triglycerides, LDL & VLDL are significantly higher in diabetic patients when compared to controls and HDL is significantly lower in cases than controls. Serum fetuin-A level is also significantly elevated in diabetic patients than controls. Pearson's correlation analysis reveals positive correlation between FBG, HbA1c, TG, TC, VLDL and fetuin-A. A negative correlation is seen between HDL and fetuin-A. However, there is no significant correlation is observed between LDL and fetuin-A. **Table: 2**

Table: 2 Correlations between Fetuin -A and Various Biochemical Parameters in Diabetic Patients

Variables	T2DM patients Pearson's correlation (r value)	p value
Fetuin-A and FBG	0.602	0.0001
Fetuin-A and HbA1c	0.721	<0.001
Fetuin-A and TC	0.408	<0.001
Fetuin-A and TG	0.269	0.007
Fetuin-A and VLDL	0.408	<0.001
Fetuin-A and LDL	0.018	0.862
Fetuin-A and HDL	-0.153	0.128

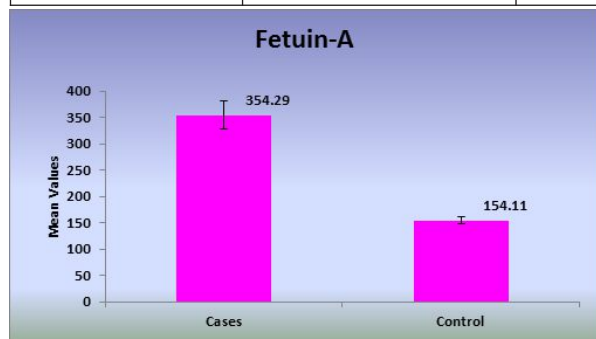


Fig 6: Comparison between Fetuin-A of cases and controls

Discussion

The increasing worldwide prevalence of type 2 diabetes mellitus and obesity has projected concerns for increasing burden of cardiovascular morbidity and mortality. ¹⁴ Fetuin-A decreased skeletal muscle glucose uptake by down regulating Akt and subsequent glucose transporter type 4 (GLUT-4) translocation to the plasma membrane. These findings point to the promoting role of fetuin-A in diabetes. ¹⁵

The results of present study show an elevated serum fetuin-A levels in newly diagnosed T2DM patients compared with healthy controls. A positive association between fetuin-A and fasting plasma glucose (r=0.602, p=0.0001) and with HbA_{1c} (r= 0.721, p=<0.001) in type 2 diabetic patients has also been observed. These findings are supported by various studies. ^{16 17, 18, 19} The association between elevated levels of fetuin-A and high risk of type 2 diabetes development is explained by mechanisms of insulin and fetuin-A actions. Fetuin-A playing the role as a inhibitor of the insulin receptor tyrosine kinase activity in muscle and in the liver, inhibits insulin signalling and introduces insulin resistance which leads to deterioration of insulin secretion and decompensation of glucose homeostasis. ²⁰ The direct correlation of fetuin-A with visceral adiposity, observed in many diabetics, may lie on casual pathway between fetuin -A and incident diabetes. ²¹ Fetuin -A secretion may be a feedback defense mechanism against vascular calcification in early stages of diabetic and atherosclerotic disease, whereas lipid disturbances and hyperinsulinemia could serve as a trigger for the hepatic fetuin-A release. ²²

Our study also showed that increased fetuin-A levels is associated with the atherogenic lipid profile in type 2 diabetes mellitus patients. We found that fetuin-A is significantly positively correlated with TG (r=0.269, p= 0.007), TC (r=0.408, p=<0.001), VLDL (r=0.408, p=<0.001) and negatively correlated with HDL (r= -0.153, p0.128), but we could not detect significant correlation with LDL (r=0.018, p=0.862). Our findings are in concordance with other studies. ^{18,21} Fetuin-A, as a phosphorylation substrate, inhibits insulin receptor tyrosine kinase activity, which results in impaired insulin action and could induce dyslipidemia by increasing lipolysis from adipose tissue. ²³ This may, in turn, lead to increased production of apolipoprotein B containing VLDL. ²⁴ Furthermore, hypertriglyceridemia may lead to a decrease in the cholesterol content of HDL, which may enhance HDL clearance from the circulation. ²⁵ Therefore, it is possible that another factor may promote the elevation in fetuin-A and LDL-cholesterol levels, i.e. transcriptional factors that regulate cholesterol homeostasis could be involved in the regulation of hepatic synthesis of fetuin-A. ²³ This finding is in contrast to our results.

In summary, higher fetuin-A levels in type 2 diabetic patients showed that there may be a cross-talk of the liver with the endocrine function of pancreas. These data support the hypothesis that fetuin-A inhibits insulin signalling by inhibiting autophosphorylation of insulin receptors.

Conclusion

We concludes that serum fetuin-A is significantly elevated in patients with type 2 diabetes mellitus when compared to healthy individuals and it indicates that serum fetuin -A may play a role in pathogenesis of diabetes by inhibiting insulin receptor tyrosine kinase and insulin signalling. Higher fetuin-A levels were also positively correlated with atherogenic lipid profile, and may be associated with future cardiovascular events in diabetic patients.

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